Organic LETTERS

Letter

pubs.acs.org/OrgLett

Synthesis of Borinic Acids and Borinate Adducts Using Diisopropylaminoborane

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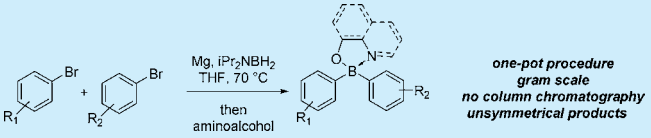
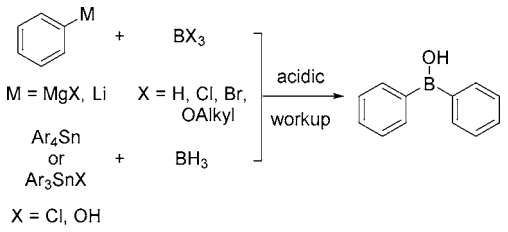
Supporting Information

ABSTRACT: *In situ* formation of aryl Grignard under Barbier condition and diisopropylaminoborane as boron source allows a complete control of the addition onto the boron electrophile. Analytically pure borinic acid derivatives were produced at the gram scale without column chromatography and isolated as borinates adducts, with ethanolamine or 8-hydroxyquinoline, after workup.



Arylboronic acids are versatile intermediates in organic synthesis.[1] They are employed in numerous systems such as Suzuki−Miyaura[2] and Chan−Evans−Lam cross coupling reactions,[3,4] Petasis reaction,[5] or transformed via functional group interconversion to halogen, carboxylic acid, phenol, and nitrile. Arylborinic acids are much less exemplified in literature.[6] They can be used as a partner in cross-coupling reactions,[7] transferring both aryl groups,[8−11] as Lewis acid catalysts,[12,13] in Ca^{2+} regulation[14,15] and OLEDs.[16] The fewer applications may be due to the relative difficulty for accessing these compounds in a selective manner. In short, most methods are currently based on the addition of strong organometallic reagents, derived mainly from magnesium or lithium, to boron based electrophiles, typically trialkylborates,[7] boron halides,[8] or diborane[12] (Scheme 1). Less employed on preparative scale is the transmetalation from tin to boron developed by Thorpe et al.[6]

Scheme 1. Borinic Acid Synthesis



Using these methods, the main issue is related to the control of the number of aryl residue transferred to the boron center. Indeed, the equilibrium between borates and boranes with reversible binding of halides and alkoxydes occurs rapidly above −50 °C or even lower. Boronic acids are hence obtained by slow addition of organometallic agent to an excess of boron electrophile. In contrast, tetraarylborates are usually prepared by extensive heating using a large excess of organometallic reagents. Borinic acids, bearing only two aryl groups, stand in between, and a 2:1 stoichiometry conducts, in most cases, a mixture of boronic and borinic acids, leading to purification issues.[17]

We envisioned that using aminoborane could lead to a difference in reactivity. Indeed, donation of the nitrogen lone pair to the boron vacancy diminishes the Lewis acidity of the boron center and reinforces the boron−nitrogen bond strength. Hence, equilibrium between borate and borane could be largely affected by this substitution. We started our investigation with diisopropylaminoborane used largely in our group as cross coupling partner.[18−23] Diisopropylaminoborane is one of the few aminoboranes that exists under a monomeric form in solution, due to the steric bulkiness of the alkyl chain preventing association in dimers, trimers, or oligomers.

Commercial phenyllithium addition to diisopropylaminoborane in THF at −78 °C followed by an acidic workup showed the formation of several species. Phenylborinic acid Ph_2BOH and phenylboronic acid $PhB(OH)_2$, respectively, resulting from the addition of two or one phenyllithium onto iPr_2NBH_2 were mainly obtained, in various proportions, as determined by ^{11}B NMR (Table S1).

As witnessed by ^{11}B NMR, a complex mixture was obtained upon addition of one equivalent of phenyl lithium **Li-2a** on aminoborane (Figure 1a). At room temperature, mostly tetracoordinated borates were observed resulting from the addition of one PhLi **Li-2a** ($[PhBH_2NiPr_2]^-Li^+$ **Li-4a**, triplet at −12.8 ppm), two PhLi ($[Ph_2BHNiPr_2]^-Li^+$ **Li-6a** doublet at −7.8 ppm), and the major compound, lithium diisopropylaminoborohydride **Li-7** observed ($[BH_3NiPr_2]^-Li^+$ quartet at −23.5 ppm). Upon addition of two equivalents of PhLi **Li-2a**, only tetravalent species were obtained (Figure 1b), with an increased amount of the diarylcompound **Li-6a**, but still in mixture with the boronic acid derivatives **Li-4a** and lithium diisopropylaminoborohydride **Li-7**. A singlet at 0 ppm, which has yet to be attributed, also appeared in a non-negligible quantity.

Received: June 3, 2015
Published: July 6, 2015

DOI: 10.1021/acs.orglett.5b01620
Org. Lett. 2015, 17, 3532−3535

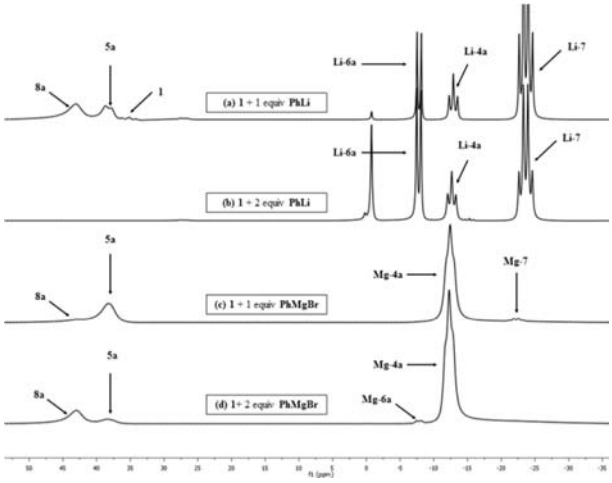
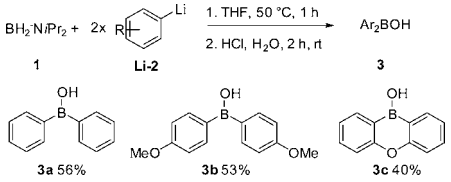


Figure 1. ^{11}B NMR study of addition of phenyllithium and phenylmagnesium bromide on diisopropylaminoborane.

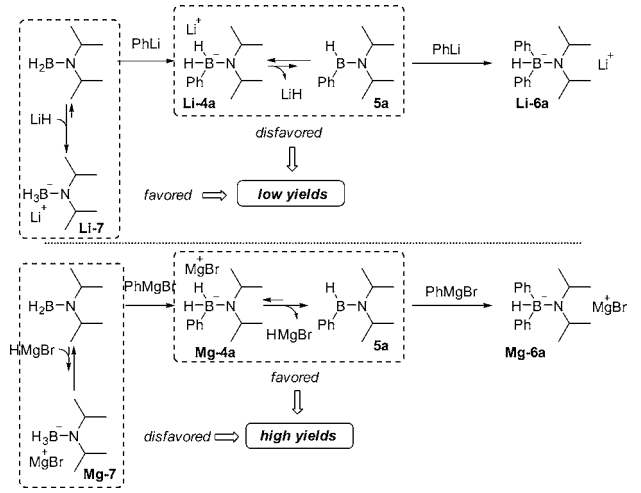
This poor selectivity was directly translated into moderate yields when the reaction was performed on preparative scale. Indeed, under optimized conditions, diphenylborinic acid **3a**, bis(4methoxyphenyl)borinic acid **3b**, and diphenyleneoxaborine **3c** were isolated only in 56%, 53%, and 40% yield, respectively (Scheme 2).

Scheme 2. Borinic Acid Synthesis Using Aryllithium



As the equilibrium between tri- and tetravalent species is governed by the substituent but also the borate countercation, we investigated magnesium derivatives behavior. Unlike phenyllithium **Li-2a**, when phenylmagnesium bromide **Mg-2a** was added to the same aminoborane, a full conversion was observed as witnessed by the disappearance of the characteristic triplet at 35 ppm of the starting material **1** (Figure 1c). The resulting mixture was mainly composed of the expected diisopropylaminophenylborohydride ($[PhBH_2NiPr_2]^-MgBr^+$ **Mg-4a,** triplet at −12 ppm) together with the aminophenylborane ($PhBHNiPr_2$ **5a**, broad doublet at 38.5 ppm) formed via elimination of HMgBr. Low amounts of diisopropylami-nodiphenylborane (Ph_2BNiPr_2 **8a**, broad singlet at 43 ppm) and magnesium diisopropylaminoborohydride were observed ($[BH_3NiPr_2]^-MgBr^+$ **Mg-7**, *q* at −22 ppm) resulting respectively from the second addition of PhMgBr **Mg-2a** and trapping of "HMgBr" by iPr_2NBH_2 **1**. The same experiment was performed using 2 equiv of PhMgBr **Mg-2a** (Figure 1d). The main product is diisopropylaminodiphenylborane (Ph_2BNiPr_2 **8a**) with the diisopropylaminephenylborohydride ($[PhBH_2NiPr_2]^-MgBr^+$ **Mg-4a**) resulting from a single PhMgBr **Mg-2a** addition. Globally, magnesium borohydride displayed a higher tendency for hydride elimination than the corresponding lithium species. Hence, after the first addition of the organometallic species, the equilibrium toward the formation of the arylaminoborane **5a** is favored in the case of magnesium and disfavored in the case of lithium (Scheme 3).

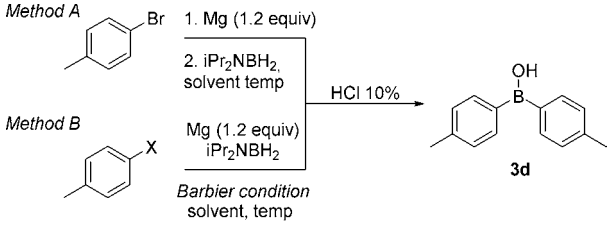
Scheme 3. Comparison between Magnesium and Lithium Species



Therefore, the second addition is facilitated in the case of the magnesium derivatives. Similarly, LiH displayed a high tendency to form the lithium aminoborohydride in the presence of the starting aminoborane (Scheme 3), diminishing the availability of boron electrophile in the mixture. Overall, Grignard reagents were found to be superior to lithium species in many aspects. This effect is currently rationalized through DFT calculation.

It is noteworthy that the addition of a third Grignard onto the diarylaminoborane has never been observed, even at high temperature, probably due to the poor reactivity of this intermediate, deactivated by the donation of the amino residue and the steric hindrance of the aryl groups. As such, the use of an excess Grignard only led to the formation of borinic acid. At refluxing THF, the addition of 4-MePhMgBr to BH_2NiPr_2 followed by hydrolysis using aqueous HCl afforded the expected borinic acid **3d** in 82% isolated yield (Table 1, entry 1). Switching to Et_2O decreased the yield to 49% (Table 1, entry 2). According to precedent in literature,[24] we attempted a one-pot protocol under Barbier conditions, and it successfully led to an excellent 96% isolated yield in THF (Table 1, entry 3) and 77% in Et_2O Table 1, entry 4). Decreasing the large excess of aryl bromide to 2.2 equiv, the borinic acid was isolated in 83% yield (Table 1,

Table 1. Optimization of the Borinic Acid Synthesis



entry	solvent	*t* (°C)	X	equiv ArX	method	yield (%)[a]
1	THF	70	Br	3	A	82
2	Et_2O	40	Br	3	A	49
3	THF	70	Br	3	B	96
4	Et_2O	40	Br	3	B	77
5	THF	70	Br	2.2	B	83
6	THF	70	I	2.2	B	60
7	THF	70	Cl	2.2	B	<40

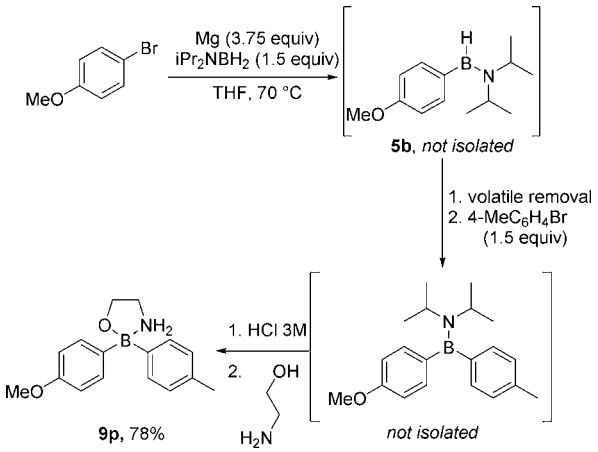
[a]Isolated yield.

DOI: 10.1021/acs.orglett.5b01620
Org. Lett. 2015, 17, 3532−3535

entry 5). In order to widen the scope of the methodology, iodides and chlorides were tested but, unfortunately, iodide led only to a moderate 60% yield (Table 1, entry 6). The generation of the Grignard reagent from aryl chlorides did not reach completion after 2 days in refluxing THF and will require a complete study (Table 1, entry 7). Noticeably, all reactions were performed on the gram scale (10 mmol).

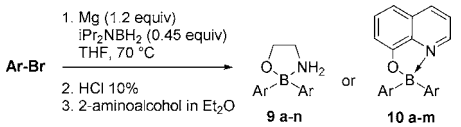
Treatment of the crude borinic acid with ethanolamine or 8-hydroxyquinoline at room temperature, gave the analytically pure borinate adducts after precipitation in Et_2O or pentane (Table 2). Some variations were done on aryl bromides with methyl and methoxy groups in meta and para positions (Table 2, entries 1−4); simple aryl groups such as naphthyl or phenyl led to good yields (Table 2, entries 5−6). Para substituted aryl Grignards with *t*-butyl groups, *n*-butyl chains, or when using 4-bromobiphenyl as starting materials gave the expected borinates in good yields (Table 2, entries 7−9). Bromodimethylarenes led to similar results, leading to bis(3,5-dimethylphenyl)borinate and bis(3,4-dimethylphenyl)borinate in 72% and 77% yield, respectively (Table 2, entries 10−11). More elaborated borinic acids were synthesized with this methodology isolated as ethanolamine adducts. 5-Bromobenzothiophene led to the corresponding borinate **9m** in 76% yield (Table 2, entry 12), and 4-bromophenyldiphenylamine led to the bis-(triphenylamine)borinate **9n** in an excellent 95% yield (Table 2, entry 13). This methodology was applied to the synthesis of active pharmaceutical ingredient **AN0128**, effective in the treatment of periodontal diseases.[25] The classical treatment by ethanolamine at the end of the reaction was replaced by a 5-hydroxy-2-pyridinecarboxylic acid in EtOH and give the desired product **9o** in 74% yield (Scheme 4). As the previous NMR study

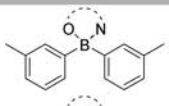
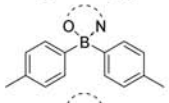
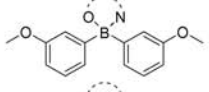
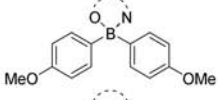
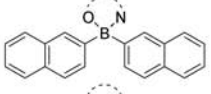
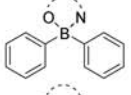
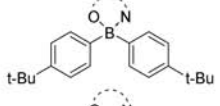
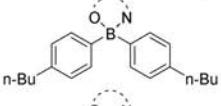
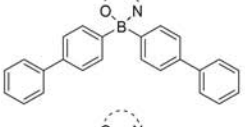
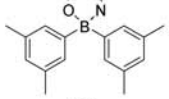
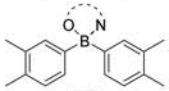
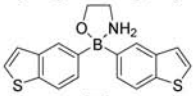
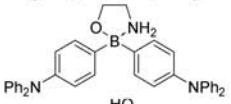
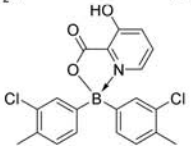
Scheme 4. Unsymmetrical Borinic Derivative Synthesis



clearly emphasized, the addition of Grignard proceeded stepwise, and we envisioned extending the scope of our methodology to the preparation of nonsymmetrical borinic acids. Reports for the preparation of such species are very scarce. In 1959, Mikhailov first reported the addition of a Grignard to a pinacol arylboronate.[26] To our knowledge, other reports[25,27,28] led to similar derivatives, using a similar approach of aryl lithium addition to pinacol boronates. Overall all previous approaches require isolation of the boronic acid and proceed in two distinct steps. As a 1:1 mixture of ArMgBr:**1** we used an excess of diisopropylaminoborane to generate arylaminoborane **5b** as a sole product. After volatile removal, a different aryl bromide reacted with the excess magnesium, leading to the diary-

Table 2. Borinate Synthesis



entry	product	yield (%)[a] cond a.[b]	cond b.[b]
1		**9e** 82	**10e** 72
2		**9d** 69	**10d** 74
3		**9f** 83	**10f** 78
4		**9b** 84	**10b** 65
5		**9g** 92	**10g** 61
6		**9a** 91	**10a** 81
7		**9h** 73	**10h** 79
8		**9i** 88	**10i** 73
9		**9j** 82	**10j** 83
10		**9k** 72	**10k** 58
11		**9l** 77	**10l** 82
12		**9m** 79	n.d.
13		**9n** 95	n.d.
14		**9o AN0128** 74[c]	

[a]Isolated yield of analytically pure borinates. [b]Cond. a: 2-amino-ethanol, 1.2 equiv, rt, Et_2O. Cond. b: hydroxyquinoleine, 1.2 equiv, rt, Et_2O. [c]5-Hydroxy-2-pyridinecarboxylic acid addition in EtOH.

laminoborane. Finally hydrolysis and aminoethanol treatment led to the nonsymmetrical borinate **9p** in 78% yield (Scheme 4).

In summary, we developed a novel procedure for the synthesis of aryl borinic acids derived in good overall yield. The method

DOI: 10.1021/acs.orglett.5b01620
Org. Lett. 2015, 17, 3532−3535

requires neither purification by column chromatography nor cryogenic conditions. Our methodology can easily provide those compounds on the multigram scale, allowing the deepest use of borinic acids in organic synthesis or electronics applications. Diisopropylaminoborane had shown a nice reactivity and selectivity providing clean borinic acids. Investigations are currently in progress to better understand the reaction mechanism and allow the synthesis of more elaborated borinic acid derivatives.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, characterizations, and NMR data. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01620.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

L.M. thanks the Région d'Aquitaine for funding. Johnson Mattey is acknowledged for a gift of transition metal halides. ANR NANOCAUSYS no. 12-CDII-0010 is acknowledged for funding; this work has been cofunded by the CNRS, Université de Bordeaux, and Conseil Régional d'Aquitaine.

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DOI: 10.1021/acs.orglett.5b01620
Org. Lett. 2015, 17, 3532−3535